

**REMARKS/ARGUMENTS**

**I. Amendments to the Specification:**

Consideration and acknowledgement by the Examiner of amendments correcting several minor errors to the specification is appreciated and it is presumed that corrections to the specification in paragraphs [0010], [0033 - 0034], [0040], [0064], [0069], [0083] and [0085] have now been entered.

**II. Status of the Claims and Amendments:**

Claims 23, 28, 37 - 39 and 43 have been amended. New claims 44 – 47 have been added to further claim that the nylon filter is a N66 nylon filter as disclosed in the specification in several places including paragraphs [0058], [0073], and [0083].

**III. Rejections under 35 U.S.C. § 103**

The Examiner's §103(a) rejection of all claims over the combination of Nochumson, Wan, Lee and Song, to the extent that such rejection may continue to be applied to the claims as amended, is respectfully traversed. All of the independent claims are directed to methods for purification of plasmid DNA that include filtration over at least one glass fiber and at least one nylon filter together with anion exchange chromatography using a TMAE resin. Independent claims 33, 37 and 43 have been amended to claim a further additional filtration step over at least one glass fiber and at least one nylon filter following anion exchange chromatography as disclosed in the specification for example in Example 5. The Examiner acknowledges that the references do not show the combination of TMAE chromatography with filtration through the specifically claimed nylon and glass filters. Such references certainly do not teach or suggest a further filtration over at least one glass fiber and at least one nylon filter following anion exchange chromatography.

Lee discloses a different plasmid purification protocol that does not teach or suggest TMAE chromatography, however, Lee is asserted to include the use of available membrane filters for removal of small debris which the Examiner asserts would include glass and nylon filters. Lee's disclosure of membrane filters for removal of small debris is then combined with Nochumson's disclosure of TMAE chromatography which admittedly does not teach or suggest use of glass fiber and nylon filtration.

It is respectfully argued that this combination of references is improper for two reasons. First, the combination is improperly asserted because no references have been cited that, alone or in combination, teach or suggest the use of filtration through the combination of at least one glass filter and at least one nylon filter in plasmid purification, thus providing no teaching with which to combine with the TMAE anion exchange chromatography reference. The Examiner has apparently concluded that, to the extent filtration to remove debris and contaminants was well known in the art, it must necessarily follow that the use of glass fiber and nylon filters would be necessarily encompassed by the prior art and can be properly combined with TMAE anion exchange chromatography to render the combination obvious. Applicant respectfully but strongly disagrees with the technical assessment and it's application to form the basis of an obviousness rejection.

The Examiner's burden of showing obviousness has not been met by merely suggesting that because glass and nylon filters existed at the time of the invention that somehow they would have been encompassed by a disclosure of the use of filters to remove debris from a lysis solution. The Examiner must show express teachings of the prior art, or the knowledge of one of ordinary skill in the art, as to the use of glass and nylon filters in endotoxin removal in order to generate a reference that can be used in a second step of properly combining with other references in conjunction with a suggestion or motivation to combine. *See In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998) ("the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.")

The present claimed invention involves a specific combination for purification of plasmid containing solutions by filtration through a series of specific media, glass fiber and nylon filters. Claims 23, 33, 37 and 43 have been amended to clarify that use of both types of filters is claimed, limitations that are even further clearly not taught or suggested by the cited art. The claimed glass fiber and nylon filters are not functioning merely as inert screens for debris and contaminants. It is believed that endotoxins are removed by binding to the glass fiber and nylon supports. Applicants surprising found that this filtration step resulted in significant purification, particularly through the removal of endotoxins, and that this step, as

well as the combined method, is of particular importance in the purification of plasmid DNA at pharmaceutical scale. The methods disclosed and claimed in the present application have been shown to be particularly effective in manufacturing plasmid preparations of high purity and yield at pharmaceutical scale as evidenced by commercial application and success in the field.

Second, even if the combination of glass and nylon filtration for removal of endotoxins from plasmid solutions was found in the prior art, it is well recognized that in order to combine asserted knowledge in the art with a prior reference, it is essential that the examiner find some reason, suggestion or motivation to combine this with the claimed TMAE anion exchange chromatography, without the benefit of hindsight. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 U.S.P.Q.2D (BNA) 1456, 1459 (Fed. Cir. 2000) (“a showing of a suggestion, teaching, or motivation to combine the prior art references is an ‘essential component of an obviousness holding’”) (quoting *C.R. Bard, Inc., v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, (Fed. Cir. 1998)); *In re Dembicza*k, 175 F.3d 994, 999 (Fed. Cir. 1999) (“Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.”). None of the asserted references teach use of glass and nylon filtration, much less for endotoxin removal, and none are directed the specific problem of endotoxin removal from plasmid DNA solutions thus providing no basis for a motivation to combine with other methodologies for this purpose. The Examiner has not identified in the prior art any suggestion or motivation to combine filtration with a series of glass fiber and nylon filters together with TMAE anion exchange chromatography in plasmid purification.

Independent claims 37 and 43 include further limitations defining plasmid purification processes that are useful for pharmaceutical scale production that include lysis by static mixing. Wan is cited as teaching bacterial lysis by static mixing. However, Wan does not teach or suggest anion exchange chromatography and does not appear to mention filtration and thus cannot suggest the claimed combinations. As previously mentioned and acknowledged by the Examiner, Nochumson does not teach or suggest glass fiber and nylon filtration for removal of endotoxins. Song teaches the theory of concentration polarization during filtration generally

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and does not teach or suggest any other limitations of the claims, including plasmid purification, anion exchange, filtration media, static mixing etc. Lee does not teach or suggest static mixing or TMAE anion exchange chromatography and, while referring to filtration generally, does not teach or suggest use of glass fiber and nylon filtration in reduction of endotoxin levels.

### Conclusion

For the reasons stated herein, the Applicant respectfully submits that independent claims 23, 33, 37 and 43 are allowable and that the dependent claims are, in turn, also allowable. Applicant respectfully requests allowance of the claims at an early date. The Commissioner is authorized to charge any additional fees incurred in this application or credit any overpayment to Deposit Account No. 50-1922. Should the Examiner have any questions, please do not hesitate to call Applicant's attorney at 832-446-2421.

Respectfully submitted,

By

Marilyn M. Huston

Marilyn M. Huston, Reg. No. 37,851

Customer No. 25746

WONG, CABELLO, LUTSCH, RUTHERFORD & BRUCCULERI, L.L.P.

20333 SH 249, Suite 600

Houston, TX 77070

(832) 446-2421

FAX (832) 446-2424

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Marilyn M. Huston

Marilyn M. Huston